

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:)	Examiner: Basi, Nirmal Singh
)	
Avi ASHKENAZI, <i>et al.</i>)	Art Unit: 1646
)	
Application Serial No. 09/909,088)	Confirmation No: 1981
)	
Filed: July 18, 2001)	Attorney's Docket No. GNE-1618 P2C79
)	
For: SECRETED AND TRANSMEMBRANE)	Customer No. 77845
POLYPEPTIDES AND NUCLEIC ACIDS)	
ENCODING SAME)	

FILED VIA EFS ON JUNE 30, 2009

**RESPONSE TO NOTICE OF NON-COMPLIANT APPEAL BRIEF AND
AMENDEDMENT OF APPELLANTS' BRIEF ON APPEAL**

MAIL STOP APPEAL BRIEF - PATENTS

Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On February 1, 2007, the Examiner made a Final rejection to pending Claims 39-47 and 49-52 and 55-58. A response and Notice of Appeal were filed on July 25, 2007. An Appeal Brief was subsequently filed on November 21, 2007.

In an Office Action mailed April 8, 2008, the Examiner withdrew the finality of the previous office action and declared prosecution reopened. As the pending claims had been twice rejected, Appellants filed a further Notice of Appeal on September 8, 2008. A Supplemental Amendment was filed concurrently with an Appeal Brief on January 8, 2009.

An Advisory Action mailed March 19, 2009 and Notification of Non-Compliant Appeal Brief mailed April 1, 2009, stated respectfully that the claim amendments submitted in the Supplemental Amendment would not be entered and the Appeal Brief incorporating the proposed amendments did not fit with the criteria of 37 C.F.R. §41.37(c)(1)(iv)).

Appellants submit herewith a further supplemental amendment cancelling those claims directed to the nucleic acid variants, putting the current claims in a better form for appeal, along with a revised brief removing arguments referring to the cancelled subject matter.

To reduce expense and duplication, Appellants hereby resubmit their Appeal Brief without the previously disclosed materials in the evidence appendix. The Board is requested to refer to the Evidence Appendix submitted with the Appeal Brief dated January 8, 2009.

The following constitutes the amended version of Appellants' Brief on Appeal.

1. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/665,350 recorded July 9, 2001, at Reel 011964 and Frame 0181.

2. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a nucleic acid encoding the polypeptide referred to herein as "PRO335." There exists two related patent applications: 1) U.S. Patent Application Serial No. 09/903,520, filed July 11, 2001 (containing claims directed to PRO335 polypeptides), and 2) U.S. Patent Application Serial No. 09/904,786, filed July 12, 2001 (containing claims directed to PRO335 antibodies). The 09/903,520 application is under non-final rejection from the same Examiner and based upon the same type of outstanding rejections. Application 09/904,786 directed to PRO335 antibodies has been allowed.

3. STATUS OF CLAIMS

Claims 1-43, 48 and 53-54 were canceled without prejudice or disclaimer.

Claims 44-47, 49-52 and 55-58 stand rejected in this application and Appellants appeal the rejection of these claims.

4. STATUS OF AMENDMENTS

Claims 39-43 have been canceled in a supplemental amendment/response to the Office Action of April 8, 2008 filed concurrently with the present Response to Notice of Non-Compliant Appeal Brief. A copy of the rejected claims in the present Appeal is provided in the Claims Appendix, incorporating the amendment.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to isolated polynucleotides comprising a nucleic acid sequence encoding the polypeptide of SEQ ID NO:290 referred to in the present application as "PRO335," a nucleic acid sequence encoding the polypeptide of SEQ ID NO:290, or a nucleic acid sequence encoding the polypeptide of SEQ ID NO:290 lacking its associated signal peptide; or the full-length coding sequence of the nucleic acid sequence of SEQ

ID NO:289; or a nucleic acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209927 (Independent Claim 44, and claims 45-47 and 49). The cDNA nucleic acid encoding PRO335 is described in the specification at, for example, page 184, line 21 to page 185, line 32 (Example 43), in Figure 101 and in SEQ ID NO:289. Page 63, lines 34-37 of the specification provides the description for Figures 101 and 102.

The invention is further directed to nucleic acids having at least 80-99% sequence identity to nucleic acids encoding polypeptides of SEQ ID NO:290; or the nucleic acid sequence encoding the polypeptide of SEQ ID NO:290 lacking its associated signal peptide; or the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:289; or the nucleic acid sequence of the cDNA deposited under ATCC accession number 209927, wherein the polypeptide encoded by said nucleic acid is an immunostimulant. PRO nucleic acid variants (Independent Claims 39-43) having at least about 80-99% nucleic acid sequence identity with a nucleic acid encoding for a full length PRO polypeptide sequence or a PRO polypeptide sequence lacking the signal peptide are described in the specification at page 55, line 2 to page 57, line 10, and for example, at page 69, line 25 to page 72, line 8.

The invention is further directed to vectors comprising these nucleic acids and host cells comprising such vectors (page 117 to page 123). The full-length PRO335 polypeptide having the amino acid sequence of SEQ ID NO:290 is described in the specification at, for example, page 50-51, lines 1-22, in Figure 102 and in SEQ ID NO:290. Hybridization probes (Independent Claim 52 and its dependents) and stringent hybridization conditions under which the nucleic acid sequences described above hybridize are described in the specification at, for example, pages 73, line 34 onwards to page 74.

Recombinant expression, characteristics and effects of the PRO335 polypeptides were disclosed in the specification, including in Examples 43, 54, 56, 74, and 77. The PRO335 polypeptides encoded by the claimed nucleic acids were shown to induce proliferation of stimulated T-lymphocytes in a mixed lymphocyte reaction as compared to controls (Example 74). PRO335 is also described as a polypeptide having homology to proteins of the leucine rich repeat superfamily, and particularly, are related to LIG-1 (page 30, line 11, to page 31, line 18, and page 110, lines 26-36). Example 74 (page 208) shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of

the proliferation of stimulated T-lymphocytes, and therefore would have utility in the treatment of conditions where the enhancement of an immune response would be beneficial. In addition, Example 77 shows the ability of PRO335 to stimulate an immune response and induce inflammation at the site of injection in the skin vascular permeability assay, using the hairless guinea pig injected with the Evans blue dye as a model system.

6. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether the data generated in the MLR assay (Example 74) satisfies the Enablement requirement set forth in 35 U.S.C. § 112, first paragraph, for the invention claimed in Claims 39-47, 49-52 and 55-58.

II. Whether the data generated in the MLR assay (Example 74) satisfies the Written Description requirement set forth in 35 U.S.C. § 112, first paragraph, for the invention claimed in Claims 39-43, 52 and 55-58.

7. ARGUMENT

Summary of the Arguments:

Issue I: Enablement

Appellants submit that patentable utility for the PRO335 polypeptide is based upon data derived from the mixed leukocyte reaction (MLR) assay. The MLR assay is a well-established and accepted assay in the art for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro*. Example 74 of the instant specification shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore has utility in the treatment of conditions where the enhancement of an immune response would be beneficial, like to treat tumor progression/ regression in cancer. In fact, the Examiner has now acknowledged that the MLR assay is an art accepted assay for identifying immunomodulatory compounds at least on page 3 and on page 11, paragraph 1 of the Final Office Action mailed February 1, 2007 and page 2 of the Office Action mailed April 8, 2008.

The Examiner's primary point to this rejection is that allegedly "the ability of the claimed PRO335 to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide for

what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not enabled by the disclosure of the instant specification.” (page 3 of the Office action mailed April 8, 2008). For support, the Examiner quotes Kahan *et al.*, Piccotti *et al.*, and Campo *et al.*, and concludes that “while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro...this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes.” (Page 4 of the Office Action mailed April 8, 2008).

Contrary to the Examiner’s assertions, Appellants submit that the instant invention is directed to a product, not a method of treatment, and the product is not required to have a specifically designated use such as for treating a particular disease, therefore, it should not be required that the claimed nucleic acids encoding the PRO335 polypeptide have to be enabled for therapeutic uses in order to meet the requirement of 35 U.S.C. 112, first paragraph.

Appellants have cancelled claims directed to the nucleic acid variants, thus rendering the rejections to Claims 39-43 moot. Claims 44-47, 49-52 and 55-58 are directed to nucleic acids that encode the polypeptide of SEQ ID NO:290 where the polypeptide has a specific and useful function (*i.e.* as “immunostimulants” useful for boosting the immune system of an animal. Appellants submit that, the instant specification, at least in Example 74, page 208, line 27, and the disclosure of the Fong declaration (submitted with Appellants’ response of August 30, 2004), describe the mixed lymphocyte reaction (MLR) assay, which the Examiner has acknowledged as sufficient to establish patentable utility under 35 U.S.C. §101 for the nucleic acids encoding the PRO335 polypeptide. The positive result for PRO335 in the MLR assay demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes.

The MLR assay of the instant application is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J.E. Coligan, A.M. Kruisbeek, D.H. Marglies, E.M. Shevach, W. Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (of record), which is referenced in Example 74. In further support of enablement based upon the MLR assay, the Declaration of Sherman Fong, Ph.D.

emphasizes that immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Costimulation of T cells can induce tumor regression and an antitumor response, both *in vitro* and *in vivo*. In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. Therefore, based on disclosures in the patent application coupled with information known in the art, one skilled in the art would know that agonistic immunostimulating polypeptides or antibodies are useful in treating, for instance, neoplastic tumors, or antagonistic antibodies – immunosuppressors, are useful for instance, in treating diseases like autoimmune or graft vs. host disease).

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present specification provides ample guidance to allow the skilled artisan to make and use the nucleic acid sequence that encodes for the PRO335 polypeptide, that are useful in the treatment of conditions like viral infections or cancer, and further, one skilled in the art would know how to use these nucleic acids without any undue experimentation.

Issue II: Written Description

Regarding the written description rejection, Appellants note that the supplemental amendment submitted concurrently with the present Response to Notice of Non-Compliant Appeal Brief and the revised brief filed herewith has cancelled those claims referring to nucleic acids with 80-99% identity to the nucleic acid defined in SEQ ID NO.: 289 and amended the dependency of Claim 55 to refer to Claim 44. Thus, the rejection of Claims 39-43 and 55-58 under 35 U.S.C. §112, first paragraph, is rendered moot.

With regard to Claim 52, directed to a fragment of the nucleic acid sequence of SEQ ID NO: 289, Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the nucleotide sequence of SEQ ID NO:289. Thus, possession of the nucleotide sequence of SEQ ID NO:289 would convey to the skilled artisan that the inventors had possession of the claimed genus of nucleic acids fragments derived from this sequence

Coupled with the general knowledge available in the art at the time of the invention, Appellants submit that the specification provides ample written support for the claimed nucleotide fragments of Claim 52. Thus, one skilled in the art would have known at the time of the invention that the Appellants had possession of the claimed nucleic acid fragments.

Detailed Arguments:

ISSUE I: The Data Generated in the MLR Assay Satisfies the Enablement Requirement of 35 U.S.C. §112, First Paragraph for Claims 39-47, 49-52 and 55-58

Cancellation of Claims 39-43 renders this rejection moot for these claims. Appellants maintain the position that Claims 44-47, 49-52 and 55-58 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Appellants' Responses dated May 17, 2005, November 3, 2006 and July 25, 2007 and Appeal Briefs dated March 10, 2006 and November 27, 2007.

A. Legal Standard for Enablement

According to 35 U.S.C. §112, first paragraph:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation^{1,2}. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is

¹ MPEP §2164.0120.

² *United States v. Teletronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

required, it is undue³. The mere fact that an extended period of experimentation is necessary does not make such experimentation undue^{4,5}.

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors (*i.e.*, the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"^{6,7} "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed⁸.

The M.P.E.P. further states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff. sub nom.*, *Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ

³ *In re Angstadt*, 537 F.2d 498,504, 190 USPQ 214, 219 (CCPA 1976).

⁴ *In re Colianni*, 561 F.2d 220,224, 195 USPQ 150, 153 (CCPA 1977).

⁵ MPEP §2164.06.

⁶ MPEP §2164.08.

⁷ *In re Marzocchi*, 439 F. 2d 220,223-4, 169 USPQ 367, 370 (CCPA 1971).

⁸ *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488,496 (Fed. Cir. 1991)).

428 (Fed. Cir. 1985) M.P.E.P. §2164.01. A considerable amount of experimentation is permissible, if it is merely routine.

B. Proper Application of the Legal Standard

Initially, Appellants submit that, both, the instant specification (in Example 74) and the Fong declaration (in previously submitted Exhibit A of the declaration) clearly refer to and incorporate by reference contents of the book "Current Protocols in Immunology, unit 3.12; edited by JE Coligan, AM Kruisbeek, DR Margulies, EM Shevach, W Stober, National Institutes of Health, Published by John Wiley & Sons, Inc. (1991) (referred to henceforth as "Current protocols"). "Current protocols" provides the detailed basic protocol, for instance, at least in Unit 3.12.6 entitled "T cell proliferation in mixed lymphocyte cultures" and further provides various other protocols for measuring T lymphocyte activation. It also provides methods for preparing cells and materials useful in the T lymphocyte activation assays and teaches that an MLR reaction can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, or, by observing blast formation, or by other methods well known in the art. Appellants submit that this information was readily available at the time of filing of the application, since the "Current protocols" reference was disclosed and incorporated by reference in its entirety at the time of filing.

Further, Appellants have provided native PRO sequence SEQ ID NO: 290. The specification also describes methods for the determination of percent identity between two amino acid sequences. In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PR0335 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences and methods of preparing the PRO polypeptides. Accordingly, one skilled in the art given the disclosure in the specification would be able to make the claimed amino acid sequence. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO: 290. Accordingly, one of ordinary skill could make the claimed invention without undue experimentation.

The Examiner's primary point to this rejection is that allegedly "the ability of the claimed PRO335 to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not enabled by the disclosure of the instant specification." (page 3 of the Office action mailed April 8, 2008). For support, the Examiner quotes Kahan *et al.*, Piccotti *et al.*, and Campo *et al.*, and concludes that "while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro...this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes." (Page 4 of the Office Action mailed April 8, 2008).

Claims 44-47, 49-52 and 55-58 are directed to antibodies to the polypeptide of SEQ ID NO:290 where the polypeptide has a specific and useful function (*i.e.* as "immunostimulants" useful for boosting the immune system of an animal. Appellants submit that, the instant specification, at least in Example 74, page 208, line 27, and the disclosure of the Fong declaration (submitted with Appellants' response of August 30, 2004), describe the mixed lymphocyte reaction (MLR) assay, which the Examiner has acknowledged as sufficient to establish patentable utility under 35 U.S.C. §101 for the nucleic acids encoding the PRO335 polypeptide. The positive result for PRO335 in the MLR assay demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes. Therefore, based on disclosures in the patent application coupled with information known in the art, one skilled in the art would know that agonistic immunostimulating polypeptides and/or antibodies are useful in treating, for instance, neoplastic tumors, or antagonistic antibodies –immunosuppressors, are useful for instance, in treating diseases like autoimmune or graft vs. host disease).

The MLR assay of the instant application is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J.E. Coligan, A.M. Kruisbeek, D.H. Marglies, E.M. Shevach, W. Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (of record), which is referenced in Example 74.

In further support of utility based upon the MLR assay, Appellants have submitted (with their Response filed August 30, 2004) the Declaration of Sherman Fong, Ph.D. As Dr. Fong

emphasizes, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Costimulation of T cells can induce tumor regression and an antitumor response, both *in vitro* and *in vivo*. In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay.

As Dr. Fong explains,

IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. IL-12 was first identified in just such an MLR [Gubler et al. PNAS 88, 4143 (1991) (Exhibit C)]. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson et al. Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)]

Dr. Fong concludes that (paragraph 10):

It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Therefore, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be used in immunoadjuvant therapy (with tumor-specific antibodies) for the treatment of tumors (cancer) and could be administered alone or together with other agents to stimulate T cell proliferation/ activation (immune function). Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the PRO335 polypeptides and its encoding nucleic acids claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

Appellants further submit that the MLR assay was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. Appellants incorporate by reference the articles and arguments presented in the Response filed November 3, 2006 (see Santoli *et al.*, J. Immunol. 137:400-407 (1986); U.S. Patent Application No. 4,950,647, Reddy *et al.* (Infect. Immun.

44:339-343 (1984); Pahwa *et al.* (Proc. Natl. Acad. Sci. USA 86:5069-5073 (1989); Kirchner *et al.* (Br. J. Clin. Pharmacol. 46:5-10 (1998); Grabstein, K.H. *et al.*, Science 264:965-968 (1994); Chapoval *et al.* (J. Immunol. 161:6977-6984 (1998); Kasaian, M.T. *et al.*, Immunity 16:559-569 (2002); Ma *et al.* (J. Immunol. 171:608-615 (2003); Naito, K. *et al.*, J. Immunol. 142:1834-1839 (1989); Tarr, P.E, Med. Oncol. 13:133-140 (1996); Gennari *et al.* (Annals of Surgery, 220:68-76 (1994); Patterson, S. *et al.*, J. Immunol. 175:5087-5094 (2005); Toura *et al.* (J. Immunol. 163:2387-2391 (1999); Tsavaris *et al.*, Br. J. Cancer 87:21-27 (2002); Amirghofran, Z. *et al.*, Irn. J. Med. Sci. 25:119-124, (2000); Abolhassani, M., Brazilian Journal of Infectious Diseases 8:382-385, (2004); U.S. Patent No. 5,817,306, filed June 7, 1995; U.S. Patent No. 5,801,193, filed April 15, 1997; U.S. Patent No. 5,958,403, filed July 11, 1994 ; and U.S. Patent No. 5,648,376, filed January 19, 1995.

Appellants further note that a positive result as a stimulator in the MLR assay is also characteristic of molecules which have known *in vivo* utilities in the treatment of disorders for which stimulation of an immune response is desirable. For example, as discussed above IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay (Gubler *et al.*, PNAS 88:4143 (1991) (submitted as Exhibit C in Appellants' Response filed August 30, 2004). In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of an approach relying on the immune stimulatory activity of IL-12 for the treatment of melanoma. Peterson *et al.*, J. Clin. Oncol. 21:2342-2348 (2003) (submitted as Exhibit D in Appellants' Response filed August 30, 2004).

Thus, the art as a whole, at the time of filing of the application, clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunostimulatory compounds and that the positive result as a stimulator in the MLR assay is widely accepted as a valid indication of therapeutic use in the treatment of disease conditions, including irradiation of tumors. Appellants note that Dr. Fong's conclusions are consistent with what is accepted in the art. Accordingly, one skilled in the art would know how to use the compounds for the asserted purpose. Therefore, based on the art's teachings about the immunostimulatory activity of molecules, as a result of a positive MLR assay, would provide sufficient correlation to one skilled in the art, such that they would use the identified compounds

in the treatment of disorders for which stimulation of the immune system is beneficial, such as viral or bacterial infections, immune deficiencies, or tumor/cancer treatments.

The Examiner asserts that "the conclusions reached by Fung-Leung et al. are based on much more experimental data, assays and testing than that provided in the instant specification and the reference does not support the position that the MLR assay in the instant specification is predictive of use as a therapeutic compound for suppressing the immune response.." (Page 6 of the Office Action mailed April 8, 2008).

Appellants submit that Appellants need not disclose every teaching found in the post-filing references. Indeed, the present specification teaches enabling disclosure for the claimed invention and the post-filing references merely confirm the feasibility of the present invention as disclosed in the specification. The pre- and post filing published papers submitted by Appellants were intended to demonstrate the MLR assay was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. In addition to the specific disclosure in the specification, general knowledge in the art at the time the invention was made also must be taken into account when assessing compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. Based on the art's teachings about the immunostimulatory activity of molecules, a result of a positive MLR assay would provide sufficient correlation to one skilled in the art, such that they would use the identified compounds in the treatment of disorders for which stimulation of the immune system is beneficial.

Appellants further point out that the instant invention is directed to a product, not a method of treatment, and the product is not required to have a specifically designated use such as for treating a particular disease, therefore, it should not be required that the claimed polypeptide has to be enabled for therapeutic uses in order to meet the requirement of 35 U.S.C. 112, first paragraph.

The Examiner asserts that Steinman and Thurner "address the utility of dendritic cells but not of a stimulatory MLR." (Page 7 of the Office Action mailed April 8, 2008).

Appellants submit that, as indicated in Unit 3.12.9 of Current Protocols in Immunology, dendritic cells are stimulator lymphocytes that induce responder T cells and activate them to

increase cytokine production, cytokine receptor expression, and ultimately proliferation of the activated T cells, all of which are measurable in different assays. In the current MLR assay, suspensions of responder T cells were cultured with irradiated- or mitomycin treated- allogenic stimulator lymphocytes and thymidine uptake was measured to give a measure of T cell proliferation (see Current protocols, Unit 3.12.9). Current Protocols also teaches how stimulator lymphocytes (which includes dendritic cells) induce responder T cells and methods of preparing them. Thus, based on this disclosure, one skilled in the art would know how to use dendritic cells in an MLR assay and how to measure T lymphocyte stimulation using thymidine uptake.

Regarding the rejection based on the Gubler reference, the Examiner alleges that it "describes the identification of IL-12 but uses MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant." (Page 7 of the Office Action mailed April 8, 2008)

Appellants respectfully disagree. The use of the MLR assay has been extensively reviewed above under utility. Several peer-reviewed references and issued patents acknowledge its usefulness (see above, utility Section I). Appellants add that in fact, the Gubler reference clearly teaches the MLR assay (see the footnote of Table 1, Fig. 3(upper panel) and related discussions in the results section), where PHA-activated lymphoblasts prepared from human PBMCs were used to measure lymphoblast proliferation in a tritiated thymidine assay. This assay was a key assay in identifying IL-12 as an immunostimulant for T lymphocytes with immunoenhancing effects. Again, this is evidenced since Gubler discloses in column 1, page 4143 that "we initiated a search for novel cytokines that would synergize with suboptimal concentrations of recombinant IL-2 **to activate cytotoxic lymphocytes *in vitro*** and thus might have **synergistic immunoenhancing effects** when administered together with recombinant IL-2 *in vivo*" (emphasis added). Thus the Gubler reference also supports the Appellants position that the MLR assay is very useful in identifying immunostimulants.

Regarding the rejection based on the Peterson reference and the use of IL-12 as an immunostimulant, the Examiner says that Peterson's subsequent research "was clearly required to suggest that the molecule could be used in this fashion". (Page 7 of the Office Action mailed April 8, 2008)

Again, Appellants respectfully disagree. Even though the Peterson's reference was published after the effective filing date of the instant application, it is an enabling reference, and its teachings are not contrary to the teachings of other references found in the art at, or before the time of filing of the instant application (July 18, 2001). For instance, Toura *et al.* (J. Immunol. 163:2387-2391 (1999); of record) disclosed that the "[i]njection of α -GalCer inhibits tumor metastasis almost completely in the liver or lung" (page 2387, col. 2). Toura *et al.* found that dendritic cells pulsed with α -GalCer are able to induce antitumor activity *in vivo* within 24 hours after cell transfer (page 2390, col. 2). Chapoval *et al.* (J. Immunol. 161:6977-6984 (1998); of record) further studied the impact of IL-15 as an adjuvant to cancer therapy using cyclophosphamide (CY) in a mouse lung tumor model. GM-CSF is used in cancer immunotherapy to expand the population of dendritic cells before reinfusion into the patient (page 136, col. 2; Tarr, P.E, Med. Oncol. 13:133-140 (1996); of record). Kirchner *et al.* (Br. J. Clin. Pharmacol. 46:5-10 (1998); of record) stated that "[t]he use of recombinant human interleukin-2 (rhIL-2) has been recommended as the best current therapy for advanced renal cell carcinoma" (page 5, col. 1). Santoli *et al.*, J. Immunol. 137:400-407 (1986); of record), and in U.S. Patent Application No. 4,950,647 (column 9, lines 30-36; Table III; of record). Based upon its immunostimulatory activity, IL-2 has been demonstrated to have a range of utilities in the treatment of immune deficiencies, as well as in immunotherapy for cancer.

The Peterson reference further supports the use of the immunostimulant IL-12 in the treatment of a cancer, namely, melanoma. As exemplified from the list of references discussed above, the use of immunostimulants in the treatment of cancer was not concluded based on the Peterson studies alone. In fact, Gubler *et al.* (discussed in the Fong Declaration) also indicates on column 1, page 4143, that "we initiated a search for novel cytokines that would synergize with suboptimal concentrations of recombinant IL-2 **to activate cytotoxic lymphocytes *in vitro*** and thus might have **synergistic immunoenhancing effects** when administered together with recombinant IL-2 *in vivo*" (emphasis added). Therefore, Peterson *et al.* is in fact a supportive and enabling reference, indicating the use of immunostimulant molecules in the successful treatment of cancer.

The Examiner cites the reference Kahan (1991) for its statement that "no in vitro assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions," (page 3 of the instant Office action). The Examiner further cites Piccotti et al. (1999) to show that "IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response in vivo" (page 3 of the instant Office action). The Examiner further cites Campo et al. (2001) and says "while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation in vitro nor produce immunosuppressive effects in vivo", (pages 3-4 of the Office Action mailed April 8, 2008).

Appellants respectfully disagree. Appellants submit that the Examiner has not correctly characterized the teachings of Kahan *et al.*, Picotti *et al.* and Campo *et al.* On the other hand, these references, in combination with those cited by Appellants, demonstrate that, the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomodulatory compounds.

For instance, the statement by Kahan *et al.* (see above) is inconsistent with what was known and accepted in the art at the time of filing regarding the MLR assay. For example, U.S. Patent No. 5,817,306 states, "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. **The results obtained from these assays are generally predictive of their *in vivo* effectiveness.**" (Column 12, lines 36-41; emphasis added). U.S. Patent No. 5,801,193, filed April 15, 1997, states that "[t]he **MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity.**" (Column 8, lines 8-10, emphasis added). U.S. Patent No. 5,648,376, filed January 19, 1995, states that "[a] measure of immunosuppression that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Column 11, lines 24-26). Therefore, Kahan's quoted statement contradicts well established scientific wisdom. As discussed extensively above, in fact, the MLR assay has been extensively used and is the best *in vitro* model for screening immunostimulatory agents. In fact, the

examiner's cited reference, Picotti *et al.*, also supports this point, since the authors extensively used the MLC assay in their studies.

Picotti *et al.* studied the mechanism of alloimmune response and graft rejections. Picotti *et al.* in fact, confirms that "IL-12 is a key cytokine involved in promoting cell mediated immune responses *in vivo*" (page 1459, col. 1). Picotti *et al.* also showed that the IL-12R gamma subunit was critical for IL-12 driven enhanced alloimmune response *in vitro and in vivo* (see abstract). Based on their studies, one skilled in the art would know that immunostimulating compounds like IL-12 (or of this invention) could be used in immunoadjuvant therapy (with tumor-specific antibodies, which is also discussed in the Fong Declaration, Petersen *et al.* reference)for the treatment of tumors (cancer). One skilled in the art would know that immunostimulant molecules can be administered alone or together with other agents to stimulate T cell proliferation/ activation (immune function) ad therefore, one skilled in the art would know that such agents can be used to stimulate an antitumor response to a tumor antigen. If anything, Picotti *et al.*, supports the point that immunostimulants are useful for treating tumors.

Appellants respectfully point out that the Examiner has misinterpreted this statement, due to the fact that the authors refer to two different types of immunosuppressive effects. Campo *et al.* set out to look for an inhibitor of MHC *in vitro* which would have the fewest side effects *in vivo* (see Abstract). The authors note that high concentrations of zinc "impair **all** T cell and monocyte function" (page 20; emphasis added). The authors took this impairment as an indicator of toxicity, and therefore intentionally used concentrations of zinc below that at which all T-cell function was impaired, in order to identify a concentration range that would not result in toxic effects. However, that does not mean that Campo *et al.* found zinc to have no immunosuppressive activity *in vivo*. In fact, the authors conclude, based upon their MLC results, that "zinc **could become an immunosuppressant in transplantation medicine** without toxic side effects" (page 21; emphasis added). Thus Campo *et al.* supports Appellants' position that those of skill in the art would interpret the results of MLC assays as having physiological relevance.

Appellants note that the Examiner has failed to point out several instances within these cited references wherein the authors stated that the MLC is an important method with a good predictive value. For example, Campo *et al.* teach that "the human mixed lymphocyte culture

(MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-gamma, **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection *in vivo*.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN-gamma **both *in vitro* and *in vivo***” (see page 18; emphasis added). Finally, Campo *et al.* teaches that “cyclosporin A, FK506, and other substances are used to prevent graft rejection. **In vitro experiments revealed an inhibition of the MLC**” (page 16). Thus the teachings of Campo *et al.* confirm that inhibition of the MLC is observed for known immunoinhibitory molecules, that are in actual clinical use.

Thus, while there are instances of unpredictability in some studies using the MLC assay, there are many more studies showing the usefulness and predictable results using MLC, as exemplified by the studies by Picotti, Landolfo and the IFN-gamma study and all the references submitted by the Appellants in this response. Therefore, the teachings within Kahan *et al.*, Piccotti *et al.*, Campo *et al.*, in fact, support the usefulness of the MLC assay.

The Examiner further asserts that “the results of the MLC assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed.” (Page 6 of the Office Action mailed April 8, 2008)

Appellants respectfully submit that enablement “is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive.” As the M.P.E.P. states, “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” The M.P.E.P. further explains that “If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied.” Appellants note that the specification

clearly indicates that the claimed polypeptides are useful in the treatment of undesirable immune responses. The use of immunosuppressive molecules in the treatment of such disorders is well known in the art, as indicated by Kahan *et al.*, Picotti *et al.* and Campo *et al.*, made of record by the Examiner, as well as the references and U.S. Patents, previously discussed and made of record by Appellants. Thus any further experimentation required for determining, for example, a particular dosage or method for the administration of PRO335 would not be considered undue.

Further, with respect to disclosure of the results of *in vitro* assays, the M.P.E.P. states that “if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995).”

The M.P.E.P. also makes it clear that the burden of proof is on the Examiner, to demonstrate lack of correlation for an *in vitro* model. “(s)ince the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example.” A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, wherein the court stated that “based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.”

As discussed above, MLR was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of

various diseases and conditions. Further, the importance of immunostimulants in the treatment of cancer or in enhancing the effectiveness of previously identified treatments for cancer, including tumor-specific antibodies were well known in the art at the time of filing of the instant application, as discussed in several references cited above. For instance, costimulation of T cells inducing tumor regression and an antitumor response, both *in vitro* and *in vivo* was known (for e.g., Steinman *et al.* -submitted as Exhibit B with the Response filed August 30, 2004). Thus, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be useful in immunoadjuvant therapies, for the treatment of tumors (cancer) and could be administered either alone or together with other agents to stimulate T cell proliferation/ activation (immune function). These could be done without undue experimentation.

The Examiner asserts that "Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls, such as for maximum response or for the inherent variability of individual responses, are provided. There is no indication of statistical significance of the results. There are no autologous controls. No correlation is provided to any particular in vivo function; there is no guidance to indicate that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV." (Page 7 of the Office Action mailed April 8, 2008)

Appellants respectfully maintain their position, as presented in the Response filed November 3, 2006, that the controls cited by the Examiner were only needed for the purpose of evaluating the properties of the stimulator cells. Such determinations, however, are not required for the MLR assay of Example 74, and thus these controls are not "essential". Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required. Further, the protocols described in the instant specification are consistent with those accepted in the art. For example, U.S. Patent No. 4,950,647, which demonstrated the immunoenhancing activity of the compound 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one using the MLR assay, did not disclose the use of any additional controls beyond those disclosed in the instant application.

With respect to the statistical significance of the results, Appellants respectfully submit that these remarks are a clear indication that the Examiner applies a heightened legal standard that is inappropriate for determining if the “enablement” standard of the Patent Statute is met. First of all, as evidenced in the numerous references made of record by Appellants, knowledge in the art at the time the invention was filed clearly demonstrate an ability to determine statistical significance of results generated from the MLR assay. Further, the MLR assay described herein is a comparative one (increases of greater than or equal to 180% is preferred), meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. Useful information is obtained when a relative differences are observed, and this is routine in biological testing. Appellants expressly assert that the observed difference for PRO335 is significant (this point is further discussed below based on U.S. Patent No. 4,950,647). For instance, Example 74 of the specification makes clear the standard to be used to determine whether a positive result in the MLR assay is significant, stating that “[p]ositive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred and that PRO335 tested positive in this assay. However, any value greater than control indicates a stimulatory effect for the test protein” (page 203, line 27). Therefore, this disclosure clearly meets the standard for statistical significance. The Examiner seems to focus on exactly how much higher (*i.e.*, requiring Appellants to provide “relative or absolute levels” and statistical analyses), but Appellants submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful.

Appellants further submit that the term “positive increases over control” would readily be understood by one skilled in the art. For instance, the Examiner’s attention is directed to U.S. Patent No. 4,950,647 (of record), which claims immunoenhancing compositions comprising the compound 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one. The immunoenhancing activity of the claimed compound was determined in part by the use of the MLR assay, as shown in Example IV (column 13, lines 20-37). The claimed compound increased the response in the MLR, with a maximum increase of 191% as compared to control, as shown in Table VII. IL-2 showed a similar level of stimulation of the MLR (with a maximum of 200% as compared to control) as shown in Table III. Thus this patent supports the threshold

of 180% described in the instant specification as showing significant stimulatory activity. Given that 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one was identified as an immunostimulatory compound based upon a reported increase in the MLR assay of 191% as compared to control, the activity for PRO335 of greater than or equal to 180% as compared to control clearly meets the standard accepted in the art as demonstrating patentable utility.

Therefore, this rejection requiring allegedly essential controls and statistical data are not appropriate, as relevant even from the art, and should be withdrawn.

As set forth in M.P.E.P. 2107 II(B)(1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utilities in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Further, the test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Teletronics, Inc.*, 857F.2d 778, 785 (Fed. Cir. 1988), Emphasis added. Thus, in addition to the specific disclosure in the specification, general knowledge in the art at the time the invention was made also must be taken into account when assessing compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. The full-length PRO335 polypeptide having the amino acid sequence of SEQ ID NO:290 is described in the instant specification at, for example, page 50-51, lines 1-22, in Figure 102 and in SEQ ID NO:290. Support for the preparation and uses of nucleic acids is found throughout the specification, including, for example pages 55-57 and 117-123.

Appellants respectfully remind the Examiner that the skilled artisan in the field of Immunology and Immunotherapeutics, at the effective filing date of November 12, 1997, would likely be a person with a Ph. D. or M.D. degree, sometimes both, with extensive experience. As such, one skilled in the art could easily test whether the PRO335 polypeptides encoded by the claimed nucleic acids can enhance T-cell stimulatory activity using the MLR assay (as described in the Example 74 of the specification and in Current Protocols). As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. §2164.01 Thus, one would have known how to make and use the present invention at the effective date of the application.

In summary, in view of the foregoing arguments, the examples and specific teachings provided in the specification and general knowledge in the art, one skilled in the art at the priority date of the present application would have clearly known how to use the invention within the full scope of the claims pending. Accordingly, Appellants respectfully request reconsideration and reversal of the enablement rejection of Claims 39-47, 49-52 and 55-58 under 35 U.S.C. §112, first paragraph.

ISSUE II: The Data Generated in the MLR Assay Satisfies the Written Description Requirement of 35 U.S.C. § 112, First Paragraph for Claims 39-43, 52 and 55-58

Claims 39-43, 52 and 55-58 are rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not describe the claimed invention in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claims invention. (Page 9 of the Office Action mailed April 8, 2008).

With the supplemental amendment filed herewith, Appellants have cancelled Claims 39-43 and amended the dependency of Claims 55-58 depend on Claim 44. Thus, the rejections of these claims are rendered moot. Coupled with the general knowledge available in the art at the time of the invention, Appellants submit that the specification provides ample written support for the claimed nucleotide fragments of Claim 52. Thus, one skilled in the art would have known at the time of the invention that the Appellants had possession of the claimed nucleic acid fragments.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is “whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language.”^{12, 13} The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.¹⁴ The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.^{15, 16}

In *Environmental Designs, Ltd. v. Union Oil Co.*,¹⁷ the Federal Circuit held, “Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.” (Emphasis added).¹⁸ Further, The “hypothetical ‘person having ordinary skill in the art’ to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art.”^{19, 20}

¹² *In re Kaslow*, 707 F.2d 1366, 1374, 212 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983).

¹³ *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991).

¹⁴ *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 U.S.P.Q.2d at 1116.

¹⁵ *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

¹⁶ *See also* M.P.E.P. §2163 II(A).

¹⁷ 713 F.2d 693, 696, 218 U.S.P.Q. 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

¹⁸ *See also* M.P.E.P. §2141.03.

¹⁹ *Ex parte Hiyamizu*, 10 U.S.P.Q.2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

²⁰ *See also* M.P.E.P. §2141.03.

B. The Disclosure Provides Sufficient Written Description for the Claimed Invention

Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the nucleotide sequence of SEQ ID NO:289. Thus, possession of the nucleotide sequence of SEQ ID NO:289 would convey to the skilled artisan that the inventors had possession of the claimed genus of nucleic acids fragments derived from this sequence and would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Appellants further point out that the instant specification identifies numerous examples of PRO DNA fragments, methods for their preparation and their intended uses. For example, paragraph [0458] of the instant specification discloses that “fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes or for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody.” Paragraph [0767] discloses that “PRO fragments may be prepared by any of a number of conventional techniques” and suggests “digesting the DNA with suitable restriction enzymes and isolating the desired fragment” and “isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR).” Paragraph [0827] goes on to suggest that “[o]ther useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences.” And paragraph [0842] discloses that “[t]he nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification.” Furthermore, paragraphs [1375] and [1376] disclose PCR primers and hybridization probes, respectively, that are specific for the PRO335 nucleic acid sequence. And paragraphs [1383] and [1384] identify the full length and disclose its deposit with the ATCC.

Therefore, Appellants submit that the specification provides ample guidance such that one of skilled in the art would know that Appellants possessed the invention as claimed in the instant claims, at the time of filing of the application. Accordingly, Appellants respectfully request reconsideration and reversal of this outstanding rejection under 35 U.S.C. §112, first

paragraph. Accordingly, Appellants respectfully request reconsideration and reversal of the written description rejection of Claims 39-43, 52 and 55-58 under 35 U.S.C. §112, first paragraph.

CONCLUSION

For the reasons given above, Appellants submit that the MLR assay disclosed in Example 74 of the specification provides at least one patentable utility for the PRO335 polypeptides of Claims 44-47, 49-52 and 55-58 meets the requirements of 35 U.S.C. §112, first paragraph - enablement and written description. Accordingly, reversal of all the rejections of Claims 44-47, 49-52 and 55-58 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 50-4634 (referencing Attorney's Docket No. 123851-181890 (GNE-1618 P2C79)).

Respectfully submitted,

Date: June 30, 2009

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8. CLAIMS APPENDIX

Claims on Appeal

44. An isolated nucleic acid comprising:
- (a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);
 - (b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide;
 - (c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290);
 - (d) the nucleic acid sequence of (SEQ ID NO: 289);
 - (e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or
 - (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927.
45. The isolated nucleic acid of Claim 44 comprising a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290).
46. The isolated nucleic acid of Claim 44 comprising a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290), lacking its associated signal peptide.
47. The isolated nucleic acid of Claim 44 comprising a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290).
49. The isolated nucleic acid of Claim 44 comprising the nucleic acid sequence of (SEQ ID NO: 289).
50. The isolated nucleic acid of Claim 44 comprising the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289).
51. The isolated nucleic acid of Claim 44 comprising the full-length coding sequence of the cDNA deposited under ATCC accession number 209927.

52. An isolated nucleic acid molecule consisting of a fragment of the nucleic acid sequence of SEQ ID NO: 289, or a complement thereof, that specifically hybridizes under stringent conditions to:

- (a) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO: 290);
- (b) a nucleic acid sequence encoding the polypeptide of (SEQ ID NO 290), lacking its associated signal peptide;
- (c) a nucleic acid sequence encoding the extracellular domain of the polypeptide of (SEQ ID NO: 290);
- (d) the nucleic acid sequence of (SEQ ID NO: 289);
- (e) the full-length coding sequence of the nucleic acid sequence of (SEQ ID NO: 289); or
- (f) the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,

wherein said stringent conditions are hybridization in 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

- 55. A vector comprising the nucleic acid of Claim 44.
- 56. The vector of Claim 55, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.
- 57. A host cell comprising the vector of Claim 55.
- 58. The host cell of Claim 57, wherein said cell is a CHO cell, an *E. coli* or a yeast cell.

9. EVIDENCE APPENDIX

1. Declaration of Sherman Fong, Ph.D. under 35 C.F.R §1.132, with attached Exhibits A-E:

A. Current Protocols in Immunology, Vol. 1, Richard Coico, Series Ed., John Wiley & Sons, Inc., 1991, Unit 3.12.

B. Steinman, R.M., "The dendritic cell advantage: New focus for immune-based therapies," *Drug News Perspect.* **13**:581-586 (2000).

C. Gubler, U. *et al.*, "Coexpression of two distinct genes is required to generate secreted bioactive cytotoxic lymphocyte maturation factor," *Proc. Natl. Acad. Sci. USA* **88**:4143-4147 (1991).

D. Peterson, A.C. *et al.*, "Immunization with melan-A peptide-pulsed peripheral blood mononuclear cells plus recombinant human interleukin-12 induces clinical activity and T-cell responses in advanced melanoma," *J. Clin. Oncol.* **21**:2342-2348 (2003).

E. Thurner, B. *et al.*, "Vaccination with Mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T-cells and induces regression of some metastases in advanced stage IV melanoma," *J. Exp. Med.* **190**:1669-1678 (1999).

2. Kahan, Barry D., "Immunosuppressive therapy," *Curr. Opin. Immunol.* **4**:553-560 (1992).

3. Picotti, J.R. *et al.*, "Interleukin-12 (IL-12)-driven alloimmune responses in vitro and in vivo," *Transplantation* **67**:1453-1460 (1999).

4. Campo, C.A. *et al.*, "Zinc inhibits the mixed lymphocyte culture," *Biological Trace Element Research*, **79**:15-22 (2001)

5. Robins *et al.* US Patent 4,950,647

6. Strobel *et al.* US Patent 5,648,376

7. Ojo-Amaize *et al.* US Patent 5,801,193

8. Haskill *et al.* US Patent 5,817,306

9. Storm et al. US Patent 5,958,403
10. Abolhassani, M., "Antibacterial effect of borage (*Echium amoenum*) on *Staphylococcus aureus*," *Brazilian Journal of Infectious Diseases* 8:382-385 (2004).
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12. Chapoval, A.I. et al., "Combination chemotherapy and IL-15 administration induces permanent tumor regression in a mouse lung tumor model: NK and T cell-mediated effects antagonized by B cells," *J. Immunol.* 161:6977-6984 (1998).
13. Fung-Leung, et al., "Tepoxalin, A Novel Immunomodulatory Compound, Synergizes with CSA in Suppression of Graft-Versus-Host Reaction and Allogenic Skin Graft Rejection", *Transplantation*, 60:362-368 (1995).
14. Gennari, R. et al., "Granulocyte macrophage colony stimulating factor improves survival in two models of gut-derived sepsis by improving gut barrier function and modulating bacterial clearance," *Annals of Surgery* 220:68-76 (1994).
15. Grabstein, K.H. et al., "Cloning of a T cell growth factor that interacts with the beta chain of the interleukin-2 receptor," *Science* 264:965-968 (1994) .
16. Kasaian, M.T. et al., "IL-21 limits NK cell responses and promotes antigen specific T cell activation: a mediator of the transition from innate to adaptive immunity," *Immunity* 16:559-569 (2002).
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Item 1 was submitted with Preliminary Amendment filed August 30, 2004, and was noted as considered by the Examiner on November 17, 2004.

Items 2-4 were made of record by the Examiner in the Office Action mailed May 30, 2006.

Items 5-22 were submitted with the Response filed November 3, 2006, and was noted as considered by the Examiner on February 1, 2007.

10. RELATED PROCEEDINGS APPENDIX

None - no decision rendered by a Court or the Board in any related proceedings identified above.

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